REMARKS

Claims 1 and 3-43 are pending. Of those claims, claims 3, 5, 9, 12-18, 21-22 and 25-43 are withdrawn. Claims 1, 5, 9, 12-14, 16 and 18 have been amended.

Applicants have amended claim 1 to specify that the tumor cells of the cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Support for this amendment is provided, for example, at specification page 4, lines 3-4; page 12, lines 18-21, page 29, lines 18-20; page 30, lines 24-26; and page 37, line 2 to page 39, line 10.

Applicants have amended claims 5, 9, 12-14, 16 and 18 to recite proper claim dependencies.

None of the amendments introduces new matter.

THE OBJECTIONS

The Claims

In the March 26, 2008 Final Office Action, the Examiner objected to claims 1, 4, 6-8, 10, 19-20, 23 and 24 because they read on non-elected embodiments of the invention and has requested appropriate correction.

Applicants respectfully submit that no correction is necessary at this time. Applicants note that they elected the species anti-OX40 antibody for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Applicants submit that claims 1, 4, 6-8, 10, 19-20, 23 and 24 are generic and encompass the elected species, anti-OX40 antibody. Accordingly, applicants request that the Examiner withdraw this objection.

New matter

In the October 27, 2008 Advisory Action, the Examiner states that the proposed amendment to claim 1 in applicants' Amendment And Reply To Office Action Pursuant To 37 C.F.R. § 1.116 filed September 26, 2008 raises the issue of new matter. The Examiner states that although the specification and the original claims appear to provide support for a cytokine-expressing cellular vaccine wherein the cell is a bystander cell or an allogeneic tumor cell, there does not appear to be sufficient support for a vaccine wherein the cell is a tumor bystander cell.

Applicants respectfully submit that the specification as filed provides ample and sufficient support for a cytokine-expressing cellular vaccine wherein the cell is a tumor bystander cell. For example, on page 30, lines 24-26, the specification states that the cytokine-expressing cellular vaccine comprises ***tumor cells*** selected from, for example, ***tumor cell lines*** (*e.g.*, ***bystander cells***). The specification states that a preferred bystander cell is the human K562 bystander cell line, which is a human erythroleukemic cell line (*see, e.g.*, page 37, line 2 to page 39, line 10; in particular, *see* page 38, lines 2-5). Accordingly, applicants request that the Examiner withdraw this new matter objection.

THE REJECTIONS

35 U.S.C. § 112, first paragraph (enablement)
Claims 1, 4, 6-8, 10, 11, 19, 20, 23 and 24

In the March 26, 2008 Final Office Action, the Examiner maintained the rejection of claims 1, 4, 6-8, 10, 11, 19, 20, 23 and 24 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that the specification does not provide a sufficient enabling description of a method for cancer therapy comprising

administering a cellular vaccine. Specifically, the Examiner states that the disclosed examples presented in applicants' previous arguments appear to be prophetic rather than working examples. The Examiner concludes that given the unpredictability of the art of cancer therapy, the skilled worker would require extensive and undue experimentation to practice the claimed invention. Applicants traverse.

Furthermore, in the October 27, 2008 Advisory Action, the Examiner states that the proposed amendment to claim 1 in applicants' Amendment And Reply To Office Action Pursuant To 37 C.F.R. § 1.116 filed September 26, 2008 raises the issue of enablement. The Examiner states that one of skill in the art is aware that bystander cells are distinct from tumor cells. Applicants also traverse.

Contrary to the Examiner's contentions, the specification discloses working examples that provides adequate enablement for the claimed invention. The specification discloses that results from animal model experiments have convincingly demonstrated that proliferation-incompetent tumor cells engineered to secrete GM-CSF are able to induce an immune response against parental, non-transduced tumor cells (*see, e.g.*, page 29, lines 8-10). The specification discloses that vaccination of proliferation-incompetent tumor cells engineered to secrete GM-CSF stimulates potent, long-lasting and specific anti-tumor immunity that prevents tumor growth in a majority of mice challenged with non-transduced tumor cells (*see, e.g.*, page 5, line 10 to page 6, line 2; page 29, line 2 to page 30, line 4; page 31, lines 21-23; page 39, line 28 to page 40, line 11; page 40, line 23 to page 41, line 2; and Figures 1A and 1B). The specification discloses administration into patients of allogeneic and autologous cancer cells engineered to secrete GM-CSF for the treatment of cancer (*see, e.g.*, page 29, line 12 to page 30, line 4).

The specification also discloses that the combination of the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent increases the efficacy of anti-tumor protection. For example, the specification discloses that, in contrast to the ineffectiveness of anti-CTLA-4 antibody monotherapy, treatment with the combination of proliferation-incompetent tumor cells that express GM-CSF and anti-CTLA-4 antibody prevented tumor growth in a majority of mice challenged with non-transduced tumor cells (*see, e.g.*, page 63, line 29 to page 64, line 20; and Figures 2A-2B). The specification also discloses that administration of the combination of proliferation-incompetent tumor cells that express GM-CSF and anti-4-1BB antibody enhanced both the number of tumor free mice and survival relative to the administration of proliferation-incompetent tumor cells that express GM-CSF alone (*see, e.g.*, page 66, line 18 to page 67, line 11; and Figures 4A-4B). The specification discloses further examples of additional combinations that demonstrate enhanced anti-tumor protection and efficacy including combinations with interferon-alpha (*see, e.g.*, page 68, line 18 to page 69, line 2; and Figures 7A-7B), docetaxel (*see, e.g.*, page 69, line 13 to page 70, line 17; and Figures 8A-8D), COX-2 inhibitor (*see, e.g.*, page 70, lines 21-27; and Figures 9A-9B), CD40 ligand (*see, e.g.*, page 71, line 29 to page 72, line 3; and Figure 11A), and anti-CD40 antibody (*see, e.g.*, page 72, line 21 to page 73, line 3; and Figures 11B-11C).

The specification also discloses that the combination of proliferation-incompetent tumor cells that express GM-CSF with OX40 ligand or anti-OX40 antibody will also increase the efficacy of anti-tumor protection (*see, e.g.*, page 73, line 8 to page 74, line 9). The specification describes that published literature and various experimental results have demonstrated a role for the engagement of OX40 (receptor) in enhancing antitumor immunity and cites to the Weinberg *et al.* publication (J. Immunol., 164:2160-2169 (2000)) (*see*, page 74, lines 4-6). Applicants respectfully submit that the Weinberg

et al. publication was cited in an Information Disclosure Statement on September 2, 2004. According to the Weinberg *et al.* publication, injection of OX40 ligand or anti-OX40 antibody in vivo during tumor priming resulted in a significant improvement in the percentage of tumor-free survivors in four different murine tumors derived from four separate tissues. Based on these results and the ample disclosure provided in the specification discussed above, one of skill in the art would recognize that administering the combination of proliferation-incompetent tumor cells that express GM-CSF with anti-OX40 antibody would result in enhanced therapeutic potency and/or efficacy relative to monotherapy.

With respect to the Examiner's statement that bystander cells are distinct from tumor cells, applicants respectfully submit that contrary to the Examiner's contention, the specification provides that bystander cells are not distinct from tumor cells. Instead, the specification provides that the cytokine-expressing cellular vaccine may comprise ***tumor cells*** selected from, for example, ***tumor cell lines*** (*e.g.*, ***bystander cells***) (*see, e.g.*, page 30, lines 24-26). Thus, the bystander cells are not distinct from tumor cells but rather, they may be tumor cells themselves.

In view of the above remarks, applicants respectfully submit that the present application provides more than adequate enablement for one skilled in the art to make and use the invention without undue experimentation. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. §§ 102(a) and (e)
Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24

In the March 26, 2008 Final Office Action, the Examiner maintained the rejection of claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24 under 35 U.S.C. §§ 102(a) and

102(e) over US Patent Publication 2003/0035790 ("Chen"). The Examiner states that Chen discloses that in a cancer vaccine approach, cancer cells are isolated from patients, transduced with the relevant genes in vitro, made proliferation-incompetent by irradiation, and administered back to the patient to enhance the patient's immune response against the tumor. The Examiner also states that Chen discloses administering anti-OX40 antibodies together with the compositions of their invention. Applicants traverse in view of the claim amendments.

Applicants have amended claim 1 (and claims dependent therefrom) to specify that the tumor cells of said cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Chen does not teach or suggest this element of the claimed invention.

Chen discloses that one approach to the treatment of metastatic carcinoma is ex vivo gene therapy or "cancer vaccine" approach (*see* paragraph [0005]). Chen discloses that in the cancer vaccine approach, cancer cells are isolated from patients, transduced with various gene vectors, expanded in vitro, and after irradiation, transplanted autologously to enhance the patient's immune response against the tumor (*see* paragraph [0005]). Thus, the cancer cells disclosed by Chen are autologous cells because they are isolated and reimplanted back into the same patient.

In contrast, the amended claims of the invention are directed to the administration of the combination of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent to a subject, wherein said tumor cells of said cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Chen does not teach or suggest this limitation of the amended claims.

Furthermore, the claimed invention also requires that the combination of the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent results in an enhanced therapeutic effect compared to monotherapy. Chen also does not teach or suggest this particular feature of the claimed invention. Therefore, Chen fails to teach or suggest each and every limitation of the amended claims. Accordingly, applicants request that the Examiner withdraw this rejection.

35 USC §101 - Nonstatutory Double Patenting
Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24

In the March 26, 2008 Final Office Action, the Examiner maintained the provisional rejection of claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24 under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-33 of copending U.S. Application No. 10/404,662.

Applicants request that this provisional rejection be held in abeyance until this application or copending application 10/404,662 is allowed. At that time, applicants will file a Terminal Disclaimer as is appropriate and proper.

CONCLUSION

In view of the foregoing remarks, applicants request that the Examiner favorably reconsider this application and allow the claims pending herein. If the Examiner believes that a telephone conference would expedite allowance of this application, she is invited to telephone the undersigned at any time.

Respectfully submitted,

/ CONNIE WONG /

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